Remarks

The present claims concern nucleic acid sequences derived from bacteriophage 77 (*Staphylococcus aureus* host). In particular, ORF104, represented by SEQ ID NO: 8, encodes an polypeptide that inhibits the host bacterium.

The specification was amended above to remove browser executable code. Claim 9 was amended to specify a minimum length of 90 nucleotides. Support for this amendment is provided in the specification, for example, on p.4, line 15, and p.10, line 23. New independent claim 73 is submitted, replacing dependent claim 10. New dependent claims 74-76 were submitted specifying inducible expression and the use of arsenite inducible operator and promoter. Support for these claims is provided, for example, in the specification on p.15, lines 1-2 and Example IV. Support for the amendments specifying 95% and 97% sequence identity is provided in the specification, for example, on p.21, lines 11-12. No new matter is added by the amendments.

Election/Restriction

Applicant notes that the Examiner has maintained the limitation to only one sequence. As discussed in Applicant's preceding Response, Applicant believes that this restriction directly contravenes the Notice of 1192 O.G. 68. Therefore, submitted herewith is a Petition to the Commissioner to compel the Group Director to follow the notice allowing the inclusion of up to 10 independent sequences in a single application. In view of that petition, Applicant has not, at this time, amended the pending claims to be limited to a single sequence.

In addition, Applicant respectfully submits that the Examiner has erroneously indicated that claims 48, 53, and 55-70 are withdraw from consideration. Each of those claims includes SEQ ID NO: 8 (note that SEQ ID NO: 8 is a part of SEQ ID NO: 10, the phage 77 genomic sequence). As each of the noted claims concerns SEQ ID NO: 8, Applicant requests that the Examiner reconsider and withdraw the indication that claims 48, 53, and 55-70 are withdrawn from consideration.

Objections to the specification

The Examiner indicated that the specification contained embedded hyperlinks. Applicant has amended the specification at the locations cited by the Examiner such that no browser-executable code is present. Therefore, Applicant requests that the Examiner withdraw this objection.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 9, 10, 12-14, 37, 39, 44, 46, 71, and 72 under 35 U.S.C. § 112, first paragraph as allegedly not being enabling for fragments or portions of SEQ ID NO: 8. Applicant respectfully traverses this rejection.

In making the rejection, the Examiner mentioned factors relevant to enablement from *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). However, while mentioning those factors, the Examiner still did not explain why one of ordinary skill in the art would not be able to practice the invention without undue experimentation. Instead, the Examiner has only provided general statements about the various *Wands* factors and a conclusory statement that undue experimentation would be involved. The issue is not how the Examiner states the *Wands* factors, but rather whether the specification provides sufficient guidance so that one of ordinary skill in the art would be able to provide the claimed nucleic acid sequences without undue experimentation. The *Wands* factors are only factors that should be considered in the enablement determination.

In this case, the Specification describes the sequence of phage 77 ORF 104 (SEQ ID NO: 8). One of ordinary skill in the art can construct fragments of such a sequences using any of a variety of known techniques (e.g., PCR-based methods). The Examiner has provided no evidence to the contrary. In addition, the Specification points out that the inhibitory effect of an encoded polypeptide can be checked by inducible expression of the sequence in bacteria (see, e.g., Examples IV and V). In addition to the inducible regulatory elements described in the Specification (i.e., the arsenite system pointed out in Example IV), one of ordinary skill in the art is aware of a number of other inducible systems that could be utilized for the inducible expression. Again, the Examiner has provided no evidence to the contrary.

Instead, the Examiner stated that there was no disclosure of the expression of ORF fragments. Applicant respectfully submits that the Examiner has ignored the way in which one

of ordinary skill in the art would view the disclosure. As one of ordinary skill in the art will recognize, fragments of the full-length ORF can be expressed using the same basic vectors and expression methods as used for the full-length ORF. Thus, the inducible systems, exemplified by the arsenite system, can be used for either full-length ORF expression or for expression of fragments of such an ORF.

Similarly, the methods used for determining whether a sequence has bacteria-inhibiting activity can be applied to both full-length polypeptides encoded by an ORF and to fragments of such polypeptides. Once again, the Examiner has not provided any evidence to the contrary.

Thus, contrary to the Examiner's assertion, one of ordinary skill in the art can construct fragments of the claimed sequences and can test polypeptides encoded by those fragments for activity without undue experimentation. Applicant therefore respectfully requests that the Examiner reconsider and withdraw these rejections.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected a number of claims under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Except as discussed below, Applicant has amended the claims to address the Examiner's concerns. Applicant submits that the amendments obviate the Examiner's objections, and therefore requests that the Examiner reconsider and withdraw the rejections. The amendments do not change the scope of the claims.

On review of the claims as originally submitted and as amended, each of claims 9, 12, and 13 already end with a period. If, on review, the Examiner believes that terminal periods are missing, Applicant requests that the Examiner point out in which paper the terminal periods are missing.

In connection with claims 9, 12, 13, and 39, the Examiner asserted that the use of the term "correspond" or "corresponding" renders the claims indefinite. Applicant respectfully submits that these terms are not, in fact, indefinite, as a definition is provided on p.21, lines 10-15. Nonetheless, in order to facilitate prosecution, the claim is amended to specify that the claimed sequence is at least 95% identical to the specified SEQ ID NO:.

Also in connection with claims 9, 12, and 13, the Examiner asserted that the term "portion" renders the claims indefinite. The Examiner appears to require that the exact portion

be specified. However, such a potentially limiting recitation is not appropriate. One of ordinary skill in the art will readily recognize that a large number of different portions of SEQ ID NO: 8 can be created using standard molecular biology techniques (e.g., using PCR-based methods), located at different positions along SEQ ID NO: 8. Thus, the term "portion" is intended to include a portion at any position along SEQ ID NO: 8 that otherwise satisfies the claim language.

In response to the Examiner's objection, claims 14 and 72 are amended to utilize the term "open reading frame" instead of "ORF".

With respect to the Examiner's objections to claims 37 and 44 as allegedly being identical, claim 44 is amended to correct the dependency to claim 10. With respect to the Examiner's assertion that claims 37 and 44 do not further limit claim 9, Applicant requests that this matter be held in abeyance until a decision on Applicant's Petition to the Commissioner concerning the inclusion of more than one sequence is decided.

In connection with the Examiner's assertion that there was insufficient antecedent basis in claim 72 for the term "ORF", Applicant submits that amendment of the claim to utilize the term "open reading frame" obviates this rejection.

The Examiner also asserted that claims 37, 44, and 47 are indefinite as there is no further limitation of the independent claim. Claims 37 and 44 were addressed above. Applicant respectfully submits that the Examiner is in error with respect to claim 47, as claim 9 specifies at least a portion, while claim 47 specifies a complete coding sequence, i.e., the complete polypeptide encoding sequence from the open reading frame. In addition, claim 47 is corrected to depend on claim 10 (now claim 73).

In view of the amendments and remarks, Applicant requests that the Examiner reconsider and withdraw these rejections.

Rejections under 35 USC 102

The Examiner rejected claims 9, 10, and 39 as allegedly being anticipated by Black et al. (N-Genseq_1101 database, Accession NO: AAT83989, August 21, 1997), asserting that Black et al. teaches a Staphylococcus aureus protein having 90.9% sequence identity to phage 77 open reading frame 104, and further asserted that the Black et al. sequence encodes a polypeptide which provides antibacterial action.

The sequence cited by the Examiner is part of Black et al., PCT/US97/02318, WO 97/30070, which describes a very large number of *S. aureus* sequences. The sequence in question is SEQ ID NO: 912. Applicant respectfully submits that the Examiner has misinterpreted the Black et al. disclosure in two ways. First, Black et al. does not described a sequence that falls within claim 9 as amended. Claim 9 specifies that the claimed sequence is at least 95% identical over at least 90 nucleotides. The Black et al. sequence cited by the Examiner does not satisfy this requirement, and therefore cannot anticipate claim 9 and similar claims.

Further, Black et al. does not describe the sequence as providing antibacterial action, Instead, both the sequence disclosure and the specification indicate that the sequence can by used to isolate antimicrobial agents and in vaccines. It is unreasonable to assert that the Black et al. sequence itself has antibacterial action, because the sequence is from the bacterium. If it were antibacterial, it would not allow the bacterium to grow. That is obviously not the case. Since claim 10 (now claim 73) requires that the nucleic acid sequence encodes a polypeptide that provides a bacteria inhibiting function that is not provided by the Black et al. sequence, the Black et al. sequence cited by the Examiner cannot anticipate claim 10 (now independent claim 73).

Indeed, Black et al. does not even identify an open reading frame within SEQ ID NO: 912 that includes present SEQ ID NO: 8 and does not provide any regulatory sequences that would provide expression from the sequence identified by the Examiner. Thus, Black et al. cannot anticipate the present claims directed to nucleic acid sequence, vectors, and cells that include regulatory components for inducible expression.

Therefore, Applicant respectfully submits that Black et al. does not anticipate any of the pending claims, and requests that the Examiner reconsider and withdraw these rejections as considered in connection with the claims as amended.

In view of the amendments and remarks above, Applicant submits that the application is now in condition for allowance, and respectfully requests a notice to that effect.

If at any time a telephone interview would be helpful to advance prosecution, the Examiner is invited to telephone the undersigned at (858) 847-6714.

No fee is believed due in connection with this communication. However, if any fee is due, kindly charge the appropriate amount to Deposit Account 50-0872.

Respectfully submitted,

Date 8 July 2002

By _____

FOLEY & LARDNER
402 West Broadway
23rd Floor
San Diego, California 92101-3542
Telephone: (619) 230-6528
Facsimile: (619) 234-3510

Wesley B. Ames
Attorney for Applicant
Registration No. 40,893

Appendix 2: Marked-up set of amended claims

9. (Three Times Amended) An isolated, purified, or enriched nucleic acid sequence at least [15] 90 nucleotides in length, wherein said sequence [corresponds] is at least 95% identical to at least a portion of a bacteriophage 77 open reading frame 17 (SEQ ID NO[.]: 4), 19 (SEQ ID NO[.]: 5), 43 (SEQ ID NO[.]: 6), 102 (SEQ ID NO[.]: 7), 104 (SEQ ID NO[.]: 8), or 182 (SEQ ID NO[.]: 9) sequence.

12. (Twice Amended) A recombinant expression vector comprising a nucleic acid sequence at least 24 nucleotides in length [corresponding] at least 95% identical to a portion of bacteriophage 77 open reading frame 17 (SEQ ID NO[.]: 4), 19 (SEQ ID NO[.]: 5), 43 (SEQ ID NO[.]: 6), 102 (SEQ ID NO[.]: 7), 104 (SEQ ID NO[.]: 8), or 182 (SEQ ID NO[.]: 9).

13. (Twice Amended) A recombinant cell comprising [a] an expression vector, wherein said vector comprises a nucleic acid sequence at least 24 nucleotides in length [corresponding] at least 95% identical to at least a portion of bacteriophage 77 open reading frame 17 (SEQ ID NO[.]: 4), 19 (SEQ ID NO[.]: 5), 43 (SEQ ID NO[.]: 6), 102 (SEQ ID NO[.]: 7), 104 (SEQ ID NO[.]: 8), or 182 (SEQ ID NO[.]: 9).

14. (Amended) The cell of claim 13, wherein [said vector is an expression vector and] expression of said [ORF] nucleic acid sequence is inducible.

39. (Amended) The nucleic acid sequence of claim 9, wherein said nucleic acid sequence [comprises] is at least [45] 120 nucleotides in length [corresponding to a said open reading frame].

47. (Amended) The nucleic acid sequence of claim [9] 73, wherein said sequence includes the complete coding sequence of said open reading frame.

48. (Amended) An isolated, purified, or enriched nucleic acid sequence at least [15] 90 nucleotides in length, wherein said sequence encodes a portion at least [5] 30 amino acids in length of a polypeptide encoded by a bacteriophage 77 open reading frame 17 (SEQ ID NO[.]: 4), 19 (SEQ ID NO[.]: 5), 43 (SEQ ID NO[.]: 6), 102 (SEQ ID NO[.]: 7), 104 (SEQ ID NO[.]: 8), or 182 (SEQ ID NO[.]: 9).

55. (Amended) An isolated, purified, or enriched nucleic acid sequence comprising a sequence at least [24] 90 nucleotides in length homologous to an equal length portion of the sequence corresponding to SEQ ID [NO.] NO: 10, wherein said sequence at least [24] 90 nucleotides in length has at least [70] 95% sequence identity to said portion.

56. (Amended) The sequence of claim 55, wherein said sequence at least [24] 90 nucleotides in length has at least [80%] 97% sequence identity.

59. (Twice Amended) The sequence of claim 58, wherein said open reading frame is open reading frame frame 17 (SEQ ID NO[.]: 4), 19 (SEQ ID NO[.]: 5), 43 (SEQ ID NO[.]: 6), 102 (SEQ ID NO[.]: 7), 104 (SEQ ID NO[.]: 8), or 182 (SEQ ID NO[.]: 9).

60. (Amended) The sequence of claim 56, wherein said sequence encodes all or a portion at least [10] 50 amino acids in length of a functional homolog of an open reading frame product of bacteriophage 77.

61. (Twice Amended) The sequence of claim 60, wherein said open reading frame is open reading frame 17 (SEQ ID NO[.]: 4), 19 (SEQ ID NO[.]: 5), 43 (SEQ ID NO[.]: 6), 102 (SEQ ID NO[.]: 7), 104 (SEQ ID NO[.]: 8), or 182 (SEQ ID NO[.]: 9).

62. (Amended) The sequence of claim 56, wherein said sequence encodes all or a portion at least 30 amino acids in length of a functional homolog [o fan] of an open reading frame product of bacteriophage 77.

63. (Twice Amended) The sequence of claim 62, wherein said open reading frame is open reading frame 17 (SEQ ID NO[.]: 4), 19 (SEQ ID NO[.]: 5), 43 (SEQ ID NO[.]: 6), 102 (SEQ ID NO[.]: 7), 104 (SEQ ID NO[.]: 8), or 182 (SEQ ID NO[.]: 9).

64. An isolated, purified, or enriched nucleic acid, wherein said sequence [corresponds] is at least 95% identical to all or a portion at least [15] 90 nucleotides in length of the sequence of SEQ ID [NO.] NO: 10.

68. (Amended) The nucleic acid sequence of claim 64, wherein said sequence [corresponds] is at least 95% identical to a portion at least 150 nucleotides in length.

69. (Amended) The nucleic acid sequence of claim [66] 64, wherein said portion at least [50] 90 nucleotides in length is all or a portion of an open reading frame.

73. (New) An isolated, purified, or enriched nucleic acid sequence comprising a sequence at least 45 nucleotides in length that is at least 95% identical to at least a portion of a bacteriophage 77 open reading frame 17 (SEQ ID NO: 4), 19 (SEQ ID NO: 5), 43 (SEQ ID NO: 6), 102 (SEQ ID : 7), 104 (SEQ ID NO: 8), or 182 (SEQ ID NO: 9) sequence., wherein said nucleic acid sequence encodes a polypeptide which provides a bacteria-inhibiting function.

74. (New) The vector of claim 72, wherein said expression is inducible using arsenite inducible operator and promoter.

75. (New) The cell of claim 13, wherein expression from said nucleic acid sequence in said expression vector is inducible.

76. (New) The cell of claim 75, wherein said expression is inducible using arsenite inducible operator and promoter.

Appendix 3: Marked-up replacement paragraphs

Replacement paragraph at p.21, lines 16-26.

In embodiments where the bacterial target of a bacteriophage inhibitor ORF product, e.g., an inhibitory protein or polypeptide, the target is preferably encoded by a *S. aureus* nucleic acid coding sequence from a host bacterium for bacteriophage 77. Target sequences are described herein by reference to sequence source sites. The sequence encoding the target preferably corresponds to a *S. aureus* nucleic acid sequence available from numerous sources including *S. aureus* sequences deposited in GenBank, *S. aureus* sequences found in European Patent Application [No.] NO: 97100110.7 to Human Genome Sciences, Inc. filed January 7, 1997, *S. aureus* sequences available from TIGR at [http://www.tigr.org/tdb/mdb/mdb.html] the Web site for which the remainder of the address after www is tigr.org/tdb/mdb/mdb.html, and *S. aureus* sequences available from the Oklahoma University *S. aureus* sequencing project at the[following URL: http://www.genome.ou.edu/staph_new.html] Web site for which the remainder of the address following www is genome.ou.edu/staph_new.html.

Replacement paragraph at p.25, line 23 to p.26, line 2.

The present invention is based on the identification of naturally-occurring DNA sequence elements encoding RNA or proteins with anti-microbial activity. Bacteriophages or phages, are viruses that infect and kill bacteria. They are natural enemies of bacteria and, over the course of evolution have perfected enzymes (products of DNA sequences) which enable them to infect a host bacterium, replicate their genetic material, usurp host metabolism, and ultimately kill their host. The scientific literature documents well the fact that many known bacteria have a large number of such bacteriophages than can infect and kill them (for example, see the ATCC bacteriophage collection at [http://www.atcc.org] the Web site atcc.org) (Ackermann and DuBow, 1987). Although we know that many bacteriophages encode proteins which can significantly alter their host's metabolism, determination of the killing potential of a given

bacteriophage gene product can only be assessed by expressing the gene product in the target bacterial strain.

Replacement paragraph at p.45, lines 6-15.

A software program was developed and used on the assembled sequence of bacteriophage 77 to identify all putative ORFs larger than 33 codons. Other ORF identification software can also be utilized, preferably programs which allow alternative start codons. The software scans the primary nucleotide sequence starting at nucleotide #1 for an appropriate start codon. Three possible selections can be made for defining the nature of the start codon: I) selection of ATG, II) selection of ATG or GTG, and III) selection of either ATG, GTG, TTG, CTG, ATT, ATC, and ATA. This latter initiation codon set corresponds to the one reported by the NCBI ([http://www.ncbi.nlm.nih.gov/htbin-post/Taxonomy/wprintgc?mode=c] at the Web site ncbi.nlm.nih.gov/htbin-post/Taxonomy/wprintgc?mode=c) for the bacterial genetic code.

Replacement paragraph at p.45, line 24 to p.46, line 6.

Sequence homology (BLAST) searches for each ORF are then carried out using an implementation of BLAST programs, although any of a variety of different sequence comparison and matching programs can be utilized as known to those skilled in the art. Downloaded public databases used for sequence analysis include:

i) non-redundant GenBank [(ftp://ncbi.nlm.nih.gov/blast/db/nr.Z)] (at the ftp site ncbi.nlm.nih.gov/blast/db/nr.Z),

ii) Swissprot [(ftp://ncbi.nlm.nih.gov/blast/db/swissprot.Z)] (at the ftp site ncbi.nlm.nih.gov/blast/db/swissprot.Z);

iii) vector [(ftp://ncbi.nlm.nih.gov/blast/db/vector.Z)] (at the ftp site ncbi.nlm.nih.gov/blast/db/vector.Z);

iv) pdbaa databases [(ftp://ncbi.nlm.nih.gov/blast/db/pdbaa.Z)] (at the ftp site ncbi.nlm.nih.gov/blast/db/pdbaa.Z);

v) [staphylococcus aureus] *Staphylococcus aureus* NCTC 8325 [(ftp://ftp.genome.ou.edu/pub/staph/staph-1k.fa)] (at the ftp site ftp.genome.ou.edu/pub/staph/staph-1k.fa);

vi) [streptococcus pyogenes] *Streptococcus pyogenes* [(ftp://ftp.genome.ou.edu/pub/strep/strep-1k.fa)] (at the ftp site ftp.genome.ou.edu/pub/strep/strep-1k.fa);

vii) [streptococcus pneumoniae] *Streptococcus pneumoniae* [(ftp://ftp.tigr.org/pub/data/s_pneumoniae/gsp.contigs.112197.Z);] (at the ftp site ftp.tigr.org/pub/data/s_pneumoniae/gsp.contigs.112197.Z);

viii) [mycobacterium tuberculosis] *Mycobacterium tuberculosis* CSU#9 [(ftp://tfp.tigr.org/pub/data/m_tuberculosis/TB_091097.Z)] (at the ftp site ftp.tigr.org/pub/data/m_tuberculosis/TB_091097.Z) and ix) [pseudomonas aeruginosa] *Pseudomonas aeruginosa* [(http://www.genome.washington.edu/pseudo/data.html)] (at the Web site genome.washington.edu/pseudo/data.html).